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(54) Title: TREATMENT OF ADDICTION DISORDERS

(57) Abstract: This invention relates to medical treatment methods for the treatment of Addiction Disorders by administering tetrahydrobenzothiazole derivatives. The present invention comprises methods for the treatment or prevention of Addiction Disorders using tetrahydrobenzothiazole derivatives, pharmaceutical compositions containing one or more of tetrahydrobenzothiazole derivatives, or pharmaceutical compositions containing one or more of tetrahydrobenzothiazole derivatives in addition to a safe and effective amount of one or more additional agents to treat related symptoms and conditions. This invention relates to new uses of tetrahydrobenzothiazoles, the enantiomers and acid addition salts thereof, particularly the pharmaceutically acceptable acid addition salts thereof with inorganic or organic acids. The invention also relates to the use of ropinirole and carbergoline for the treatment of Addiction Disorders.

TREATMENT OF ADDICTION DISORDERS

This invention was made in part with government support under grant 5RO1DA12048 awarded by the National Institutes of Health. The government has certain rights in the invention.

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/170,104 filed on December 10, 1999, herein incorporated by reference in its entirety.

Background of the Invention

This invention relates generally to medical treatment methods. Specifically, the invention relates to methodology for the treatment of Addiction Disorders by administering tetrahydrobenzothiazole derivatives.

The prevalence of addictions and drug use and abuse worldwide, especially in the United States, has reached epidemic levels. There are a plethora of drugs, both legal and illegal, the abuse of which have become serious public policy issues affecting all strata of society with its obvious medical and social consequences. Some users live in an extremely high-risk population associated with poverty and illegal

activity. Other users who might classify themselves as recreational users are at risk due to (a) properties of the drug(s) which make them addictive, (b) a predisposition of the user to become a heavy user or (c) a combination of factors including personal circumstances, hardship, environment and accessibility. Adequate treatment of drug abuse, including polydrug abuse, requires innovative and creative programs of intervention.

Three especially problematic drugs of addiction are cocaine, alcohol and nicotine. Cocaine is an alkaloid derived from the leaves of the coca plant (*Erythroxylon coca*). In the United States alone, there currently are more than 5 million regular cocaine users of whom at least 600,000 are classified as severely addicted. Within this population, a significant number of addicts actively are seeking therapy. For example, in 1990, 380,000 people sought medical treatment for cocaine addiction and the number is increasing. At that time, it was estimated that 100,000 emergency room admissions per year involve cocaine use. The cumulative effects of cocaine-associated violent crime, loss in individual productivity, illness, and death are an international problem.

The lack of effective therapies for the treatment of drug addiction strongly suggests that novel approaches must be developed. Up to now there is no commercially available drug for the therapeutic treatment of drug addiction with proven evidence of efficacy across different classes of abused drugs. Surprisingly and unexpectedly, it has been found that tetrahydrobenzothiazole derivatives, e.g., pramipexole, are useful for treatment of addiction disorders.

Pramipexole is a dopamine-D3/D2 agonist the synthesis of which is described in European Patent 186 087 and its counterpart, U.S. Pat. No. 4,886,812. It is known

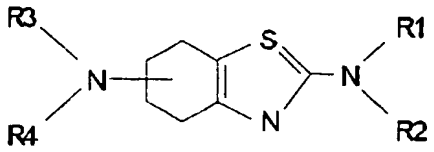
primarily for the treatment of schizophrenia and Parkinson's disease. It is known from German patent application DE 38 43 227 that pramipexole lowers the plasma level of prolactin. Further, it is known from German patent application DE 39 33 738 that pramipexole can be used to decrease abnormal high levels of thyroid stimulating hormone (TSH). U.S. Pat. No. 5,112,842 discloses the transdermal administration of the compounds and transdermal systems containing these active compounds. WO patent application PCT/EP93/03389 describes the use of pramipexole as an antidepressant agent.

Brief Summary of the Invention

It is an object of the present invention to describe the use of tetrahydrobenzothiazole derivatives for the treatment of Addiction Disorders.

The present invention comprises methods for the treatment or prevention of Addiction Disorders using the compounds of formula (I), pharmaceutical compositions containing one or more of the compounds of formula (I), or pharmaceutical compositions containing one or more of the compounds of formula (I) in addition to a safe and effective amount of one or more additional agents to treat related symptoms and conditions.

This invention relates to new uses of tetrahydrobenzthiazoles of the general formula (I):



(I)

the enantiomers and acid addition salts thereof, particularly the pharmaceutically acceptable acid addition salts thereof with inorganic or organic acids.

In general formula I above:

R1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkenyl or alkynyl group each having 3 to 6 carbon atoms, an alkanoyl group having 1 to 6 carbon atoms, a phenyl alkyl or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the above mentioned phenyl nuclei may be substituted by 1 or 2 halogen atoms,

R2 represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms,

R3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 7 carbon atoms, a phenyl alkyl or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the phenyl nucleus may be substituted by fluorine, chlorine or bromine atoms,

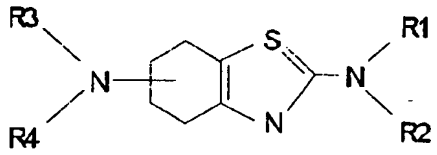
R4 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms or

R3 and R4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group.

Detailed Description of the Invention

The present invention comprises methods for the treatment or prevention of Addiction Disorders using the compounds of formula (I), pharmaceutical compositions containing one or more of the compounds of formula (I), or pharmaceutical compositions containing one or more of the compounds of formula (I) in addition to a safe and effective amount of one or more additional agents to treat related symptoms and conditions. In the preferred embodiments, the methods of use are for the treatment wherein the Addiction Disorder is a Substance Use Disorder.

This invention relates to the treatment or prevention of Addiction Disorders using tetrahydrobenzthiazoles of the general formula (I):



(I)

In general formula I above:

R1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkenyl or alkynyl group each having 3 to 6 carbon atoms, an alkanoyl group having 1 to 6 carbon atoms, a phenyl alkyl or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the above mentioned phenyl nuclei may be substituted by 1 or 2 halogen atoms,

R2 represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms,

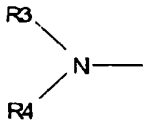
R3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 7 carbon atoms, a phenyl alkyl or

phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the phenyl nucleus may be substituted by fluorine, chlorine or bromine atoms,

R4 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms or

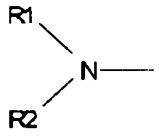
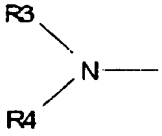
R3 and R4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group.

Preferred compounds of general formula I above are those wherein the group

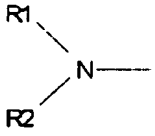


is in the 5 or 6-position.

As examples of the definitions of the groups

 and 

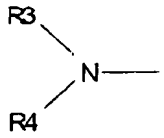
The



group represents an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methylisopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, N-methylallylamino, N-ethyl-allylamino, N-n-propylallylamino, N-n-butyl-allylamino, propargylamino, N-

methyl-propargylamino, N-n-propyl-propargylamino, formylamino, acetylamino, propionylamino, butanoylamino, hexanoylamino, N-methyl-acetylamino, N-allyl-acetylamino, N-propargyl-acetylamino, benzylamino, N-methyl-benzylamino, 2-chloro-benzylamino, 4-chloro-benzylamino, 4-fluoro-benzylamino, 3,4-dichloro-benzylamino, 1-phenylethylamino, 2-phenylethylamino, 3-phenyl-n-propylamino, benzoylamino phenacetylamino or 2-phenylpropionylamino group

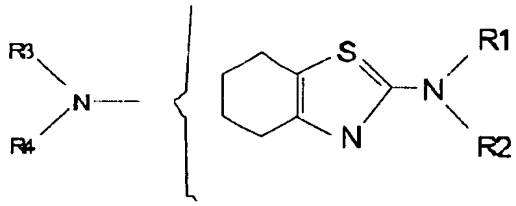
and the group



represents an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, n-heptylamino, dimethylamino, diethylamino, di-n-propylamino, Di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, diallylamino, N-methyl-allylamino, N-ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-allylamino, propargylamino, butin-2-ylamino, hexin-2-ylamino, dipropargylamino, N-methyl-propargylamino, N-ethyl-propargylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, N-methyl cyclohexylamino, N-ethyl-cyclohexylamino, formylamino, acetylamino, propionylamino, butanoylamino, pentanoylamino, hexanoylamino, heptanoylamino, N-methyl-acetylamino, N-ethyl- acetylamino, N-n-propyl-acetylamino, N-allyl- acetylamino, benzoylamino, fluorobenzoylamino, chlorobenzoylamino, bromobenzoylamino, phenylacetamino, 2-

phenylpropionylamino, N-methyl- benzoylamino, N-ethyl-chlorobenzoylamino, Dichlorobenzoylamino, N-cyclohexyl-acetylamino, benzylamino, chlorobenzylamino, bromobenzylamino, 1-phenylethylamino, 2-phenylethylamino, 2-phenyl-n-propylamino, 3-phenyl-n-propylamino, N-methyl-benzylamino, N-ethyl-benzylamino, N-ethyl-chlorobenzylamino, N-ethyl-2-phenylethylamino, N-acetyl-benzylamino, N-acetyl-chlorobenzylamino, N-allyl-benzylamino, N-allyl-chlorobenzylamino, pyrrolidino, piperidino, hexamethyleneimino or morpholino group.

Particularly preferred compounds of general formula I are, however, the compounds of general formula Ia [See Original Patent for Chemical Structure Diagram]



(Ia)

wherein

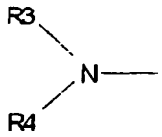
R1 represents a hydrogen atom, an alkyl group having 1 to 3 carbon atoms, an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichloro-benzyl or phenylethyl group,

R2 represents a hydrogen atom, a methyl or ethyl group,

R3 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms, an allyl, propargyl, benzyl, chlorobenzyl, phenylethyl, cyclopentyl or cyclohexyl group,

R4 represents a hydrogen atom, an alkyl group having 1 to 3 carbon atoms or an allyl group or

R3 and R4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group, but particularly the compounds wherein the group



is in the 6-position, and the acid addition salts thereof, particularly the pharmaceutically acceptable acid addition salts.

The most preferred compound is pramipexole. By pramipexole is meant 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole, its (-)-enantiomer thereof, and pharmacologically acceptable salts thereof.

The synthesis, formulation and administration of the compounds of formula I is described in U.S. Pat. Nos. 4,843,086; 4,886,812; 5,112,842; and 5,650,420, which are incorporated in their entirety herein by reference.

The Addiction Disorder (compulsive disorder) to be treated in the present invention may be any disorder characterized by irresistible impulsive behavior. Examples of compulsive disorders treatable by the methods of the present invention include, without limitation, substance use disorders, eating disorders, pathological gambling, paraphilias/sexual addictions.

As used herein, the term "substance use disorders" includes substance dependence or abuse with or without physiological dependence. The substances associated with these disorders are: alcohol, amphetamines (or amphetamine-like

substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (or phencyclidine-like compounds), sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of all of the above.

Preferably, the compulsive disorder is a substance use disorders. More preferably, the substance use disorders is cocaine, alcohol or nicotine dependence.

In particular, the term "substance use disorders" includes drug withdrawal disorders such as alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances. It will be appreciated that reference to treatment of nicotine withdrawal includes the treatment of symptoms associated with smoking cessation.

Other "substance use disorders" include substance-induced anxiety disorder with onset during withdrawal; vulnerability even after long periods of absence to environmental trigger induced craving; substance-induced mood disorder with onset during withdrawal; and substance-induced sleep disorder with onset during withdrawal.

Besides substance use disorders, other Addiction Disorders include pathological gambling, paraphilias/sexual addictions, compulsive overeating and obesity. In fact, a common genetic anomaly in the dopamine D2 receptor has been found among people with alcoholism, cocaine dependence, nicotine dependence, pathological gambling, compulsive overeating and obesity (U.S. Pat. No. 5,621,133).

Like ethanol and other drugs of abuse, food can produce euphoria or pleasure when consumed.

Pathological gambling also has many affinities to drug dependence. Clinicians have remarked on the similarity between the aroused euphoric state of the gambler and the "high" of the cocaine addict or substance abuser.

"Eating disorder" refers to compulsive overeating, obesity or severe obesity. Obesity means body weight of 20% over standard height-weight tables. Severe obesity means over 100% overweight.

"Pathological gambling" is a condition characterized by a preoccupation with gambling. Similar to psychoactive substance abuse, its effects include development of tolerance with a need to gamble progressively larger amounts of money, withdrawal symptoms, and continued gambling despite severe negative effects on family and occupation.

"Treating" or "Treatment" refer to: (i) preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

In relation to substance use disorders, "treating" refers to suppressing the psychological addiction or physical tolerance to the drug of abuse, and relieving or preventing a withdrawal syndrome resulting from the drug dependence.

Substance (e.g., nicotine, opioid and alcohol) dependence is a cluster of cognitive, behavioral and physiological symptoms demonstrating there is a continuing

use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that results in tolerance, withdrawal and compulsive substance-taking behavior.

Tolerance is the need for significantly increased amounts of the substance to achieve the desired effect, or a markedly diminished effect with continued use of the same amount of the substance.

Generally, withdrawal is a behavioral change, having physiological and cognitive components, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing withdrawal symptoms, an individual is likely to take the substance to relieve or avoid those symptoms.

As used herein, the term "mammal" means the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes therapeutic and prophylaxis of the symptoms and named condition and amelioration or elimination of the conditions once it has been established.

As used herein, the term "opioid" means any natural opioid (opiate), semisynthetic and synthetic exogenous substance that binds to one or more opioid receptor subtype and produces agonist action. The three known opioid receptor subtypes include mu, kappa and delta. Examples of opioids include opium, morphine, heroin, codeine, pentazocine, buprenorphine, meperidine, butorphanol, feutanyl, nalbuphine, hydromorphone, oxycodone, oxymorphone and methadone.

As used herein, the term "withdrawal" or "cessation and withdrawal" shall refer to symptoms and conditions resulting from: diminished or discontinued

administration and use of tobacco products, diminished and discontinued administration and use of nicotine, diminished or discontinued administration and use, injection or orally, of one or more opioid, diminished or discontinued administration and use of ethanol, and any combination of two or more thereof. Such nicotine, opioid, and ethanol withdrawal symptoms and conditions are characterized in the DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (1994). The DSM-IV was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

The criteria for substance dependence set forth in DSM-IV is a pattern of substance use, leading to clinically significant impairment or distress as manifested by at least three selected from the following group, occurring at any time within the same twelve month period: (1) tolerance as defined by either (a) a need for substantially increased amounts of the substance to achieve the desired effect; or (b) substantially diminished effect with continued use of the same amount of the substance; (2) withdrawal, as demonstrated by either (a) the characteristic withdrawal syndrome for the specific substance; or (b) the same, or a closely related substance is taken to relieve or avoid withdrawal symptoms; (3) the substance is often taken in larger amounts or over a longer period then was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities to obtain the substance, use the substance, or recover from its effects; (6) important social, occupational or recreational activities are given up or

reduced because of substance use; and (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Substance dependence can be with physiological dependence; that is evidence of tolerance or withdrawal is present, or without physiological dependence, where no evidence of tolerance or withdrawal is present.

Four of the conditions include remission. These types of remission are based on the interval of time that has elapsed since the cessation of dependencies and whether there is continued presence of one or more of the symptoms included in the criteria for dependencies.

The qualifier "early full remission" is used when for at least one month, but for less than twelve months, no symptom of dependence has been met.

The qualifier "early partial remission" is used when for at least one month but less than 12 months, one or more symptoms for dependence has been met, but the full criteria for dependence has not been met.

The term "sustained full remission" is used when none of the symptoms of dependence have been met at any time during a period of twelve months or longer.

The term "sustained partial remission" is used if the symptoms for dependence have not been met for a period of twelve months or longer, however, one or more symptom for dependence has been met.

The qualifier "on agonist therapy" is used if the subject is on a prescribed agonist medication and no symptom for dependence has been met for that class of medication for at least the past month. It also applies to those being treated for dependence using a partial agonist.

The term "in a controlled environment" is used if the subject is in an environment where access to substances of abuse are restricted and no symptom for dependence has been met for at least the past month.

With substance withdrawal, the essential feature is the development of a substance-specific behavioral change, with physiology and cognitive concomitants, which is due to the cessation of, or reduction in, heavy and prolonged substance use. The substance-specific symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. These symptoms are not due to a general medical condition and are not better accounted for by another mental disorder. Withdrawal usually, but not necessarily, is associated with substance dependence. Individuals with withdrawal have a craving to re-administer the substance to reduce these symptoms. Withdrawal develops when doses of the substance are reduced or stopped.

Therefore, the term "cessation and withdrawal" shall include, but is not limited to, the following conditions characterized in the DSM-IV: Nicotine Withdrawal; Nicotine -Related Disorder Not otherwise Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, without physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; Nicotine Dependence, Sustained Partial Remission; Nicotine Dependence, On Agonist Therapy; Opioid Withdrawal; Opioid-Related Disorder Not Otherwise Specified; Opioid Dependence, with physiological dependence; Opioid Dependence, without physiological dependence; Opioid Dependence, Early Full Remission; Opioid Dependence, Early Partial Remission; Opioid Dependence, Sustained Full Remission;

Opioid Dependence, Sustained Partial Remission; Opioid Dependence On Agonist Therapy; and Opioid Dependence in a controlled environment; Ethanol Withdrawal; Ethanol Dependence with Physiological Dependence; Ethanol Withdrawal, without Physiological Dependence; Ethanol Withdrawal, Early Full Remission; Ethanol Withdrawal, Early Partial Remission; Ethanol Withdrawal, Sustained Full Remission; Ethanol Withdrawal, Sustained Partial Remission; Ethanol Withdrawal, on Agonist Therapy; and Ethanol Withdrawal, In a Controlled Environment.

The present method is also helpful to those who have replaced, or partially replaced, their use of tobacco with the use of nicotine replacement therapy. Thus, such patients can be assisted to reduce and even eliminate entirely their dependence on nicotine in all forms.

The method of the present invention is preferably administered in connection with and/or subsequent to an educational and/or behavioral modification program to enhance continued abstinence from tobacco, opioids, ethanol, or combinations thereof. The method of the present invention is also highly beneficial to such programs by alleviating the suffering experienced from the nicotine, opioid, and ethanol withdrawal over the course of such programs. Therefore, the programs can be more effective by focusing on educational and behavioral modification goals, further reducing the incidence of program non-completion.

"Pharmaceutically acceptable salt" refers to a salt of the inventive compounds which possesses the desired pharmacological activity and which is neither biologically nor otherwise undesirable. The salt can be formed with inorganic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate,

dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, thiocyanate, tosylate and undecanoate. Examples of a base salt include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine and lysine. The basic nitrogen-containing groups can be quarternized with agents including lower alkyl halides such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides such as benzyl and phenethyl bromides.

"Stereoisomers" refers to isomers that differ only in the way the atoms are arranged in space. "Isomers" are different compounds that have the same molecular formula. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers that are not mirror images of each other. "Racemic mixture" is a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

The compounds of formula I include the various individual isomers as well as the racemates thereof. For treating Addiction Disorders (AD's), a compound of formula (I) will generally be employed at a daily dosage in the range of from about 0.05 mg to about 10 mg administered orally, for an average adult human. Preferably,

the daily dosage is from about 0.25 mg to about 5mg per day and most preferably it is from about 0.25 mg to about 2.5 mg per day.

A preferred treatment disclosed here for the treatment or prevention of Addiction Disorders comprises the administration of a therapeutically effective amount of one or more of the compounds named pramipexole, ropinirole, and cabergoline including their pharmaceutically acceptable derivatives, analogs, salts and bases.

The chemical name for cabergoline is 1((6-allylergolin-8.beta-yl) -carbony.)-1-(3-(dimethylamino)propyl)-3-ethylurea. Carbergoline is the active ingredient in DOSTINEX.RTM. or CABASER.RTM. Tablets, sold in the United States, Europe and Latin America as a treatment for hyperprolactinemic disorders and/or as a treatment for Parkinson's disease. The synthesis and use of cabergoline is disclosed and claimed in U.S. Pat. No. 4,526,892, which is incorporated herein by reference.

The chemical name for ropinirole is 4-›2-(dipropylamino)ethyl-1,3-dihydro-2H-indol-2-one. Ropinirole is an indolone derivative and includes derivatives, analogs and pharmaceutically acceptable salts thereof. These indolone derivatives are described in U.S. Pat. No. 4,452,808 to Gallagher, Jr., issued Jun. 5, 1984, and in U.S. Pat. No. 4,912,126 to Owen, issued Mar. 27, 1990, both of which are incorporated herein by reference.

All of these compounds and combinations should be administered in pharmaceutically effective amounts as determined by titration or methods ordinarily used by those skilled in the art.

The Addiction Disorder (compulsive disorder) to be treated in the present invention include substance use disorders, eating disorders, pathological gambling, paraphilias/sexual addictions.

Preferably, the Addiction Disorder is a compulsive disorder. Preferably, the compulsive disorder is a substance use disorders. More preferably, the substance use disorders is cocaine, alcohol or nicotine dependence.

For treating Addiction Disorders (AD's), one or more of the compounds pramipexole, ropinirole, and cabergoline including their pharmaceutically acceptable derivatives, analogs, salts and bases, will generally be employed at a daily dosage in the range of from about 0.05 mg to about 10 mg administered orally, for an average adult human. Preferably, the daily dosage is from about 0.25 mg to about 5mg per day and most preferably it is from about 0.25 mg to about 2.5 mg per day.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. In the event that the response in a subject is insufficient at the above doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example 24 hours or multiple doses per day is contemplated to achieve appropriate systemic levels of compounds.

To prepare the pharmaceutical compositions of this invention, one or more tetrahydrobenzothiazole compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water,

glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

The pharmaceutical compositions herein will contain, per dosage unit, *e.g.*, tablet, capsule, powder injection, teaspoonful, suppository and the like from about 0.05 mg to about 10 mg of the active ingredient.

The activity of the compounds of formula I in treating AD's was first evidenced in clinical studies conducted to evaluate the efficacy of tetrahydrobenzothiazoles in treating idiopathic Parkinson's Disease.

Examples of specific compounds of formula (I) arc: 2-amino-6-dimethylamino-4,5,6,7-tetrahydrobenzthiazol-dihydrochloride, 2-amino-6-pyrrolidino-4,5,6,7-tetrahydrobenzthiazol-dihydrochloride, 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzthiazol-dihydrochloride, 2-allylamino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride, 6-[N-ally-N-(4-chloro-benzyl)-amino]-2-amino-4,5,6,7-tetrahydro-benzthiazol- dihydrochloride and

2-amino-6-diallylamino-4,5,6,7-tetrahydrobenzthiazol-dihydrochloride and the pharmaceutically acceptable salts thereof.

Included within the scope of this invention are the various individual anomers, diastereomers and enantiomers as well as mixtures thereof. Such compounds are included within the definition of formula (I). In addition, the compounds of this invention also include any pharmaceutically acceptable salts, for example: alkali metal salts, such as sodium and potassium; ammonium salts; monoalkylammonium salts; dialkylammonium salts; trialkylammonium salts; tetraalkylammonium salts; and tromethamine salts. Hydrates and other solvates of the compound of the formula (I) are included within the scope of this invention.

Pharmaceutically acceptable salts of the compounds of formula (I) are prepared by reacting the tetrahydrobenzothiazole of formula (I) with the appropriate base and recovering the salt.

The tetrahydrobenzothiazole derivatives may be used in conjunction with one or more other drug compound and used according to the methods of the present invention so long as the pharmaceutical agent has a use that is also effective in treating AD's and/or concurrent illnesses. It is not intended that the category be limited by the specific examples. Those of ordinary skill in the art will be able to identify readily those pharmaceutical agents that have utility with the present invention. Those of ordinary skill in the art will recognize also numerous other compounds that fall within the categories and that are useful according to the invention.

Pharmaceutical agents include the following categories: adrenergics, adrenocortical steroids, adrenocortical suppressants, aldosterone antagonists, amino

acids, analeptics, analgesics, anorectic compounds, anorexics, anti-anxiety agents, antidepressants, antihypertensives, anti-inflammatorys, antinauseants, antineutropenics, antiobsessional agents, antiparkinsonians, antipsychotics, appetite suppressants, blood glucose regulators, carbonic anhydrase inhibitors, cardiotonics, cardiovascular agents, choleretics, cholinergics, cholinergic agonists, cholinesterase deactivators, cognition adjuvants, cognition enhancers, hormones, memory adjuvants, mental performance enhancers, mood regulators, neuroleptics, neuroprotectives, psychotropics, relaxants, sedative-hypnotics, serotonin antagonists, serotonin inhibitors, serotonin receptor antagonists, stimulants, thyroid hormones, thyroid inhibitors, thyromimetics, cerebral ischemia agents, vasoconstrictors, and vasodilators.

Specifically, tetrahydrobenzothiazoles may be administered in combination with other medications to treat certain symptoms and disorders including:

I. Treatment of cocaine abuse/dependence with catecholaminergic, serotonergic, glucocorticoid, glutamatergic and gabanergic agents.

II. Treatment of overweight/obesity condition with sibutramine (MERIDIA); psychostimulants, (*e.g.*, d-amphetamine, phentermine) and orlistat.

III. Treatment of nicotine addiction/smoking cessation with bupropion (ZYBAN), serotonin reuptake inhibitors, nicotine patches and gum, and other antidepressants.

IV. Treatment of alcohol abuse/dependence (alcoholism) with naltrexone (REVIA), serotonin reuptake inhibitors, and other antidepressants.

V. Treatment of other behavioral addictions with serotonin reuptake inhibitors, lithium, valproic acid or divalproex sodium (*e.g.*, DEPAKENE or DEPAKOTE), other antidepressants, naltrexone, atypical antipsychotics, (*e.g.*, olanzapine (ZYPREXA), quetiapine (SEROQUEL), risperidone (RISPERDAL), ziprasidone) and other mood stabilizers (*e.g.*, carbamazepine)

VI. Treatment of paraphilias/sexual addictions with serotonin reuptake inhibitors, lithium, divalproex sodium/valproic acid, antiandrogen medications (*e.g.*, medroxyprogesterone, gonadotropin-releasing hormone (GnRH) agonists), other antidepressants, and other mood stabilizers (*e.g.*, carbamazepine).

When administered, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); boric acid and a salt (0.5-2.5% W/V); and phosphoric acid and a salt (0.8-2% W/V). Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V).

In the present invention, the tetrahydrobenzothiazoles derivatives are administered in safe and effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition being treated. In general, an effective amount for treating an AD will be that amount necessary to inhibit mammalian symptoms of the particular AD in-situ. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a minimum dose be used, that is, the lowest safe dosage that provides appropriate relief of symptoms.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state(s) being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such

modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above.

The present invention further relates to transdermal therapeutic systems that contain as active substance tetrahydrobenzothiazole, e.g., 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole or the (-)-enantiomer thereof (SND 919, Pramipexole). The nature and structure of the transdermal therapeutic system should not be regarded as critical, provided that the excipients and carriers used are compatible with the active substances described according to the invention and the active substance is released in a quantity sufficient to achieve the desired therapeutic effect.

Systems suitable for transdermal administration are known from the prior art. Thus, for example, U.S. Pat. No. 3,558,122 discloses a transdermally therapeutic system comprising a backing layer that is impervious to the active substance, a reservoir of active substance and means for fixing the system to the skin. This system may contain special devices, e.g. a membrane, for controlling the release of active substance. A method of producing a transdermal system in the form of a polyacrylate film is known from European Patent 86 997. In another embodiment according to the invention, the active substance may also be administered by means of an ionophoretic system. Systems of this kind are known in the art. Although the solution to the present problem is not limited to the use of a specific system-provided that the system ensures an adequate release of active substance-systems which have an active substance

reservoir consisting of an emulsion polymerized polyacrylate are preferred according to the invention. Such systems are known in the art. Using the systems described in these patents it is possible to administer tetrahydrobenzothiazoles, e.g., 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole or the (-)-enantiomer thereof (SND 919) in a effective amount.

In a preferred embodiment, the system according to the invention consists of a backing layer which is impervious to the active substance and is simultaneously formed as a covering plaster to secure the system to the skin, a reservoir containing the active substance and a removable protective film which protects the system before it is ready to be used. The preferred carrier material is polyacrylate. The proportion of active substance in this reservoir is between 5 and 30% by weight, the preferred range being between 7 and 15% by weight.

Example.

A subject with a primary diagnosis of DSM IV cocaine dependence is treated with a single dose of 0.25 mg dose of pramipexole. Medication is given 1 hour before presentation of cocaine cues designed to resemble environmental triggers of cocaine craving. Measurements are taken at time points; precue, postcue and 1 hour postcue. The subject is shown a 5-minute cocaine-cue videotape containing a complex mixture of auditory and visual cues specific to crack cocaine. Psychological measures are assessed using the Within Session Rating Scale to evaluate craving for cocaine. This instrument asks patients to estimate the intensity of craving and a variety of other drug-related states on a 100 mm visual analogue scale. Above appropriate numbers on the scale are the adjective modifiers not at all, mildly, moderately, and extremely. Questions concerning cocaine

craving include, "During this session, how much did you desire or crave cocaine?" and "If you had access to cocaine during this session, how likely would you have been to use it?". In addition, the subject is rated for visual analogue scales of anxiety similar to those previously shown to be capable of detecting rapid changes during panic attack provocation. Anxiety is measured by averaging three items that reflect the subjects anxiety level; ratings of irritability, anxiety and nervousness on the visual analogue scales. The increase in craving measured is significantly less than when treated with placebo.

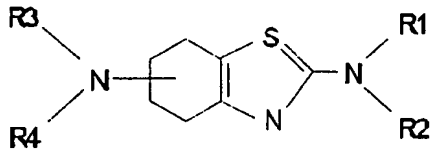
All publications and patents are herein incorporated by reference to the same extent as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

Many variations of the present invention within the scope of the appended claims will be apparent to those skilled in the art once the principles described herein are understood.

CLAIMS

What is claimed is:

1. A method for treating an Addiction Disorder comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:



(I)

wherein

R1 is selected from the group consisting of a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 3 to 6 carbon atoms, an alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 6 carbon atoms, a phenyl alkyl or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the above mentioned phenyl nuclei may be substituted by 1 or 2 halogen atoms,

R2 is selected from the group consisting of a hydrogen atom and an alkyl group with 1 to 4 carbon atoms,

R3 is selected from the group consisting of a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 7

carbon atoms, and a phenyl alkyl or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part where the phenyl nucleus may be substituted by fluorine, chlorine or bromine atoms,

R4 is selected from the group consisting of a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, and an alkenyl or alkynyl group having 3 to 6 carbon atoms

or

R3 and R4 together with the nitrogen atom between them represent a group is selected from the group consisting of a pyrrolidino, piperidino, hexamethyleneimino and a morpholino group.

2. The method of claim 1 wherein the compound is selected from the group consisting of a compound of the formula I wherein:

R1 and R2, together with the nitrogen atom between them, represent a group selected from the group consisting of an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methylisopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, N-methylallylamino, N-ethyl-allylamino, N-n-propylallylamino, N-n-butyl-allylamino, propargylamino, N-methyl-propargylamino, N-n-propyl-propargylamino, formylamino, acetylamino, propionylamino, butanoylamino, hexanoylamino, N-methyl-acetylamino, N-allyl-acetylamino, N-propargyl-acetylamino, benzylamino, N-methyl-

benzylamino, 2-chloro-benzylamino, 4-chloro-benzylamino, 4-fluoro-benzylamino, 3,4-dichloro-benzylamino, 1-phenylethylamino, 2-phenylethylamino, 3-phenyl-n-propylamino, benzoylamino phenacetylamino, and 2-phenylpropionylamino groups

and wherein

R3 and R4, together with the nitrogen atom between them, represent a group selected from the group consisting of an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, n-heptylamino, dimethylamino, diethylamino, di-n-propylamino, Di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, diallylamino, N-methyl-allylamino, N-ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-allylamino, propargylamino, butin-2-ylamino, hexin-2-ylamino, dipropargylamino, N-methyl-propargylamino, N-ethyl-propargylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, N-methyl cyclohexylamino, N-ethyl-cyclohexylamino, formylamino, acetylamino, propionylamino, butanoylamino, pentanoylamino, hexanoylamino, heptanoylamino, N-methyl-acetylamino, N-ethyl-acetylamino, N-n-propyl-acetylamino, N-allyl- acetylamino, benzoylamino, fluorobenzoylamino, chlorobenzoylamino, bromobenzoylamino, phenylacetamino, 2-phenylpropionylamino, N-methyl- benzoylamino, N-ethyl-chlorobenzoylamino, Dichlorobenzoylamino, N-cyclohexyl-acetylamino, benzylamino, chlorobenzylamino, bromobenzylamino, 1-

phenylethylamino, 2-phenylethylamino, 2-phenyl-n-propylamino, 3-phenyl-n-propylamino, N-methyl-benzylamino, N-ethyl-benzylamino, N-ethyl-chlorobenzylamino, N-ethyl-2-phenylethylamino, N-acetyl-benzylamino, N-acetyl-chlorobenzylamino, N-allyl-benzylamino, N-allyl-chlorobenzylamino, pyrrolidino, piperidino, hexamethyleneimino and morpholino group;

and the acid addition salts, isomers and racemates thereof.

3. The method of claim 1 wherein the compound is selected from the group consisting of compounds of the formula I wherein:

R1 is selected from the group consisting of a hydrogen atom, an alkyl group having 1 to 3 carbon atoms, an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichloro-benzyl and a phenylethyl group,

R2 is selected from the group consisting of a hydrogen atom, a methyl and an ethyl group,

R3 is selected from the group consisting of a hydrogen atom, an alkyl group with 1 to 6 carbon atoms, an allyl, propargyl, benzyl, chlorobenzyl, phenylethyl, cyclopentyl and a cyclohexyl group,

R4 is selected from the group consisting of a hydrogen atom, an alkyl group having 1 to 3 carbon atoms and an allyl group

or

R3 and R4 together with the nitrogen atom between them represent a group is selected from the group consisting of pyrrolidino, piperidino, hexamethyleneimino and a morpholino group.

and the acid addition salts, isomers and racemates thereof.

4. The method of claim 3 wherein R3 and R4 together with the nitrogen atom between them is in the 6-position.

5. The method of claim 1 wherein the compound of formula I is pramipexole.

6. The method of claim 1 wherein the Addiction Disorder is selected from the group consisting of pathological gambling, pyromania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, eating disorders characterized by binge eating, and substance use disorders.

7. The method of claim 5 wherein the Addiction Disorder is selected from the group consisting of pathological gambling, pyromania, compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, eating disorders characterized by binge eating, and substance use disorders.

8. The method of claim 7, wherein the therapeutically effective amount is from about 0.05 mg to about 10 mg per day.

9. The method of claim 7, wherein the therapeutically effective amount is from about 0.25 mg to about 5mg per day.

10. The method of claim 7, wherein the therapeutically effective amount is from about 0.25 mg to about 2.5 mg per day.

11. The method of claim 8 wherein the compound is used in conjunction with one or more other drug compounds selected from the group consisting of adrenergics, adrenocortical steroids, adrenocortical suppressants, aldosterone antagonists, amino acids, analeptics, analgesics, anorectic compoundss, anorexics, anti-anxiety agents, antidepressants, antihypertensives, anti-inflammatorys, antinauseants, antineutropenics, antiobsessional agents, antiparkinsonians, antipsychotics, appetite suppressants, blood glucose regulatorss, carbonic anhydrase inhibitors, cardiotonics, cardiovascular agents, choleretics, cholinergics, cholinergic agonists, cholinesterase deactivators, cognition adjuvants, cognition enhancers, hormones, memory adjuvants, mental performance enhancers, mood regulators, neuroleptics, neuroprotectives, psychotropics, relaxants, sedative-hypnotics, serotonin antagonists, serotonin inhibitors, serotonin receptor antagonists, stimulants, thyroid hormones, thyroid inhibitors, thyromimetics, cerebral ischemia agents, vasoconstrictors, and vasodilators.

12. The method of claim 5 wherein the Addiction Disorder is an eating disorder and the compound is used in conjunction with one or more other drug

compounds selected from the group consisting of serotonin re-uptake inhibitors, antidepressants, psychostimulants, and orlistat.

13. The method of claim 5 wherein the Addiction Disorder is an overweight/obesity condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of sibutramine, psychostimulants, and orlistat.

14. The method of claim 5 wherein the Addiction Disorder is a nicotine addiction condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of bupropion, serotonin reuptake inhibitors, nicotine, and antidepressants.

15. The method of claim 5 wherein the Addiction Disorder is an alcohol abuse/dependence condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of benzodiazepines, acamprosate, naltrexone, serotonin reuptake inhibitors, and other antidepressants.

16. The method of claim 5 wherein the Addiction Disorder is a behavioral addiction condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of serotonin reuptake inhibitors, lithium, valproic acid or divalproex sodium, other antidepressants, naltrexone, atypical antipsychotics, and other mood stabilizers.

17. The method of claim 5 wherein the Addiction Disorder is a paraphilias/sexual addiction condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of serotonin reuptake inhibitors, lithium, divalproex sodium/valproic acid, antiandrogen agents, other antidepressants, and other mood stabilizers.

18. The method of claim 5 wherein the Addiction Disorder is a opioid addiction condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of opioids, opioid antagonists and alpha-adrenergic agents.

19. A method for treating an Addiction Disorder comprising administering to a mammal afflicted with such condition a therapeutically effective amount of one or more compounds selected from the group consisting of the compounds ropinirole, cabergoline and their pharmaceutically acceptable derivatives, analogs, salts and bases.

20. The method of claim 19 wherein the Addiction Disorder is a disorder selected from the group consisting of substance use disorders, eating disorders, pathological gambling, and sexual addictions.

21. The method of claim 20 wherein the Addiction Disorder is a substance use disorders.

22. The method of claim 21 wherein the substance use disorder is selected from the group consisting of cocaine dependence, alcohol dependence and nicotine dependence.

23. The method of claim 21 wherein the substance use disorder is cocaine dependence.

24. The method of claim 21 wherein the substance use disorder is alcohol dependence.

25. The method of claim 21 wherein the substance use disorder is nicotine dependence.

26. The method of claim 20, wherein the therapeutically effective amount is from about 0.05 mg to about 10 mg per day.

27. The method of claim 25, wherein the therapeutically effective amount is from about 0.25 mg to about 5mg per day.

28. The method of claim 19 wherein the compound is used in conjunction with one or more other drug compounds selected from the group consisting of adrenergics, adrenocortical steroids, adrenocortical suppressants, aldosterone antagonists, amino acids, analeptics, analgesics, anorectic compoundss, anorexics, anti-anxiety agents, antidepressants, antihypertensives, anti-

inflammatorys, antinauseants, antineutropenics, antiobsessional agents, antiparkinsonians, antipsychotics, appetite suppressants, blood glucose regulatorss, carbonic anhydrase inhibitors, cardiotonics, cardiovascular agents, choleretics, cholinergics, cholinergic agonists, cholinesterase deactivators, cognition adjuvants, cognition enhancers, hormones, memory adjuvants, mental performance enhancers, mood regulators, neuroleptics, neuroprotectives, psychotropics, relaxants, sedative-hypnotics, serotonin antagonists, serotonin inhibitors, serotonin receptor antagonists, stimulants, thyroid hormones, thyroid inhibitors, thyromimetics, cerebral ischemia agents, vasoconstrictors, and vasodilators.

29. The method of claim 19 wherein the Addiction Disorder is an eating disorder and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of sibutramine, psychostimulants, and orlistat.

30. The method of claim 19 wherein the Addiction Disorder is a nicotine dependence condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of bupropion, serotonin reuptake inhibitors, nicotine, and antidepressants.

31. The method of claim 19 wherein the Addiction Disorder is an alcohol dependence condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of

benzodiazepines, acamprosate, naltrexone, serotonin reuptake inhibitors, and other antidepressants.

32. The method of claim 19 wherein the Addiction Disorder is an opioid dependence condition and the compound is used in conjunction with one or more other drug compounds selected from the group consisting of opioids, opioid antagonists and alpha-adrenergic agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/33444

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/428, 31/437, 31/4045
US CL :514/367, 418, 288

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/367, 418, 288

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	Database on STN, Accession Number 1997:168007, CAINE et al., 'D. sub. 3 receptor test in vitro predicts decreased cocain, self-administration in rats; abstract, Neuro Report, 1997, 8/910, pages 2373-2377.	1, 3, 4, 5-7, 18 --- 8-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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